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Amyloidosis in Retinal Neurodegenerative Diseases

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As a part of the central nervous system, the retina may reflect both physiological processes and abnormalities related to pathologies that affect the brain. Amyloidosis due to the accumulation of amyloid-beta (A β) was initially regarded as a specific and exclusive characteristic of neurodegenerative alterations seen in the brain of Alzheimer's disease (AD) patients. More recently, it was discovered that amyloidosis-related alterations, similar to those seen in the brain of Alzheimer's patients, also occur in the retina. Remarkably, these alterations were identified not only in primary retinal pathologies, such as age-related macular degeneration (AMD) and glaucoma, but also in the retinas of Alzheimer's patients. In this review, we first briefly discuss the biogenesis of A β , a peptide involved in amyloidosis. We then discuss some pathological aspects (synaptic dysfunction, mitochondrial failure, glial activation, and vascular abnormalities) related to the neurotoxic effects of A β . We finally highlight common features shared by AD, AMD, and glaucoma in the context of A β amyloidosis and further discuss why the retina, due to the transparency of the eye, can be considered as a "window" to the brain.

Keywords: Alzheimer's disease, age-related macular degeneration, glaucoma, neurodegeneration, synaptic and mitochondrial dysfunction, microangiopathy, neuroinflammation

INTRODUCTION

Pathological alterations, such as synaptic dysfunctions, neuronal cell loss, inflammatory responses, microvasculature abnormalities, mitochondrial failure, and oxidative stress, have been associated with amyloid-beta (A β) in the brain. However, similar pathological alterations have more recently also been reported in the retina where they may mirror analogous events occurring in the brain (1). The present review will focus on these aforementioned aspects of A β 's deleterious effects but does not have the ambition to cover all aspects of A β cytotoxicity. For instance, the issues related to aberrant A β clearance will not be discussed here since they have been recently extensively reviewed elsewhere [e.g., Ref. (2)].

Retinal accumulation of A β is broadly recognized as being involved in amyloidosis-associated neurodegeneration. Pathological hallmarks of amyloidosis are related to the accumulation of specific types of proteins, including A β , prone to oligomerize with a high content of beta (β)-sheet structures (3). Among the neurodegenerative diseases related to A β amyloidosis, Alzheimer's disease (AD) is certainly the best known and the most studied. More recently, it has been recognized that A β -related amyloidosis also occurs during glaucoma and age-related macular degeneration (AMD). Historically and up to very recently, AD was considered as an exclusively cerebral disorder, while glaucoma and AMD were regarded as neurodegenerative disorders specific to the retina. However,

it is increasingly clear that AD-like pathological alterations seen in the brain also occur in the retina (4), where they may even start earlier. Conversely, the pathological phenomena observed in glaucoma, for example, are associated with neurodegeneration of selected brain areas (5). Altogether, this new evidence suggests that the retina may be used as the “window” to the brain for the study of the earliest pathophysiological changes involved in neurodegeneration. This attractive idea is behind different aspects of amyloidosis that will be discussed here.

Parkinson's disease (PD), which shares many features of A β -amyloidosis with AD, glaucoma, and AMD, will not be discussed here, and we recommend a number of excellent and exhaustive reviews on this topic (6, 7). Indeed, although PD is considered an amyloidosis-associated disease, involving the accumulation of both A β and α -synuclein, the relevant fibrils have not been identified in the PD retina (8). This is in sharp contrast with the presence of A β plaques, identical to those found in AD-vulnerable brain areas that have been identified in the retina (9, 10). Furthermore, A β -amyloidosis seen in PD is sometimes considered as an epiphenomenon to the oligomerization of α -synuclein into structures known as Lewy bodies. Consequently, rigorous analysis of alterations specific to A β -amyloidosis in PD would require a systematic comparative follow-up of cohorts composed of “mixed” PD (displaying both α -synuclein and A β -amyloidosis) and “pure” PD (displaying exclusively α -synuclein amyloidosis). Such studies, similar to the one reported by Bertrand and colleagues (11), are still relatively scarce. Finally, there is no consensus about the precise type of pathological alterations in the PD retina, since thickening (12), thinning (13), and absence of change (14) in the retinal nerve fiber layer (RNFL) have all been reported. The analysis of retinal A β -amyloidosis in PD would therefore be more complicated. By consequence, this review will focus only on AD, glaucoma, and AMD.

BIOLOGY OF AMYLOID- β AND ITS PRECURSOR APP

Amyloid precursor protein (APP), a type 1 transmembrane glycoprotein, belongs to a family of proteins, which in mammals include APP-like protein-1 (APLP1) and APP-like protein-2 (APLP2) (15). Despite the widespread expression of the APP gene in mammalian and non-mammalian cells, the physiological role of APP is still unclear. APP-related mRNA has been found not only in the nervous system but also in the immune system, muscles, and other organs, such as the pancreas, lung, and kidney (16, 17). Alternative splicing of APP mRNA gives rise to multiple isoforms, which are differentially expressed among various tissues and different stages of development. In particular, APP is upregulated during brain development, and specific APP variants are associated with neurite outgrowth and synaptogenesis (18, 19).

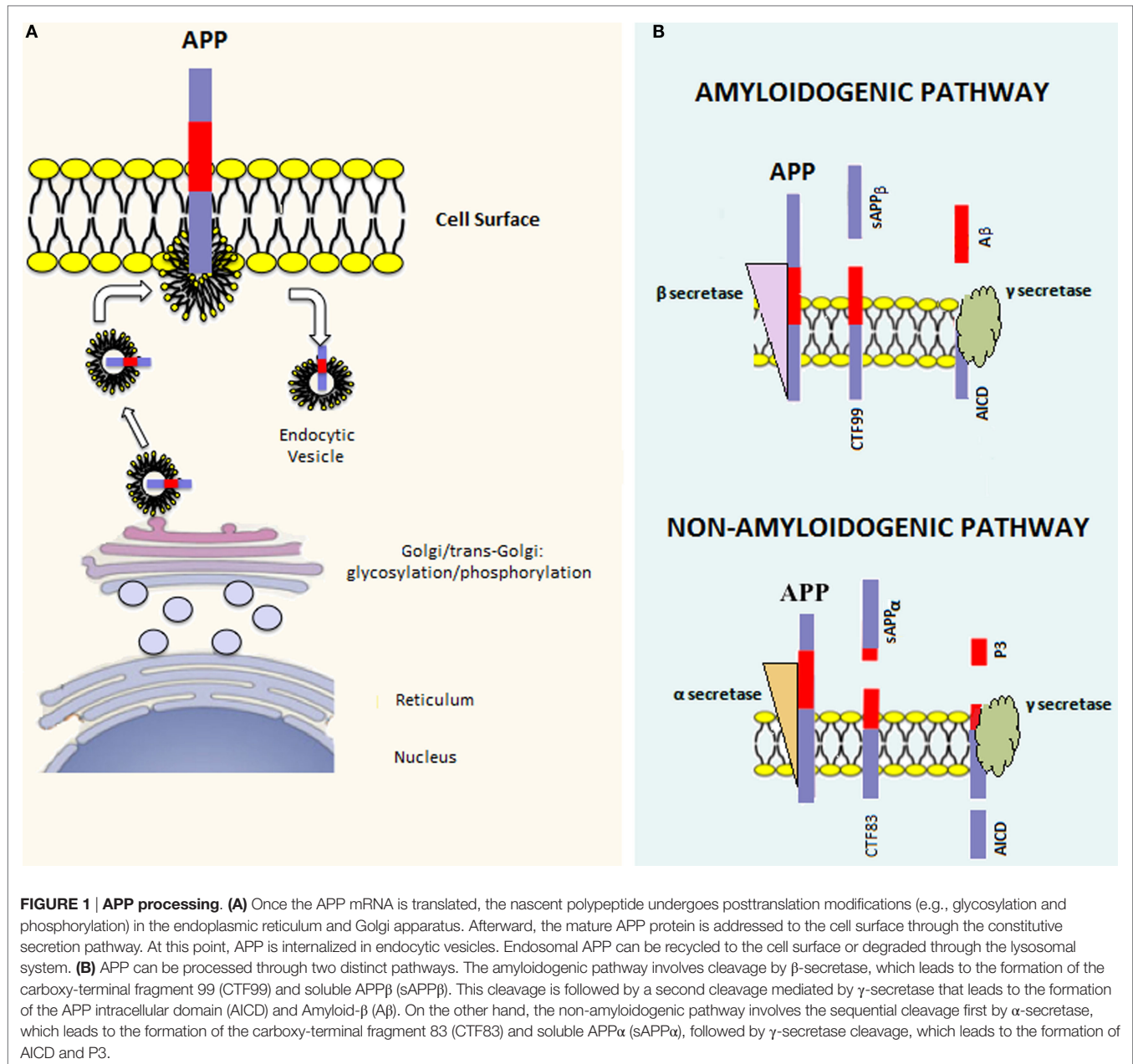
There are three major APP isoforms, APP770, APP751, and APP695, which are all generated from the alternative splicing of exons 7 and/or 8. APP695 is mainly neuronal, whereas the other two variants are principally non-neuronal (20). APP polypeptides undergo posttranslational modifications (such as glycosylation and phosphorylation) and are subsequently addressed to the plasma membrane *via* the constitutive secretory pathway

(Figure 1A). Successively, APP is internalized through clathrin-mediated endocytosis and reaches the endosomal system. Part of endosomal APP is recycled to the cell surface, whereas another conspicuous part is degraded in lysosomes (21, 22). In the steady state, APP is preferentially localized in the Golgi and in the trans-Golgi network, and only a tiny fraction is localized on the cell surface.

Amyloid precursor protein can be posttranslationally processed through two distinct pathways [reviewed in Ref. (23)] (Figure 1B). The amyloidogenic pathway involves sequential cleavage steps by β -secretase and γ -secretase, which generates A β . The second pathway, which is predominant, involves sequential cleavage steps by α -secretase and γ -secretase but does not yield A β . Indeed, α -secretase cleavage occurs within the A β peptide region, preventing A β formation. It has been shown that proteases belonging to the A-disintegrin and metalloproteinase (ADAM) family have α -secretase activity (24–26). Since ADAMs are cell surface proteins, α -secretase cleavage likely occurs at the level of the plasma membrane and involves the membrane pool of APP (27). α -secretase cleavage leads to the formation of an amino-terminal fragment called secreted APP (sAPP) α and a carboxy-terminal fragment called CTF83. β -secretase is a type 1 transmembrane protease, and its cleavage leads to the formation of sAPP β and CTF99. In converse to α -secretase cleavage, β -secretase cleavage occurs mainly in endocytic vesicles and not at the cell surface, where both β -site APP cleaving enzyme-1 (BACE1) and APP are swiftly recycled. The first cleavage step is followed by γ -secretase cleavage in both pathways. The latter is a protein complex composed of at least four proteins: presenilin (PS) 1 or 2, nicastrin, presenilin enhancer 2 (Pen 2), and anterior pharynx defective 1 (Aph-1) (28). γ -secretase processes CTF83 and CTF99, yielding the APP intracellular domain (AICD) plus the fragment p3 and AICD plus A β , respectively. A β peptides of different lengths, from 38 to 43 amino acids, can be generated by γ -secretase cleavage; however, A β 1–42 and A β 1–40 are considered to be the most relevant forms to amyloidosis.

Since APP undergoes sequential cleavage steps, it has been difficult to distinguish the physiological role of APP from those of its cleavage products. Generally, the role of APP in the brain is regarded as beneficial and often associated with its cleavage product, sAPP α . It has been shown that APP promotes cell proliferation, neuronal stem cell differentiation, neurite outgrowth, synaptogenesis, cell adhesion, and regulates long-term potentiation (LTP). APP-KO mice are viable and fertile, suggesting that APP – or its products – are not essential for development or alternatively, are part of a network of proteins with redundant functions (29). However, APP-deficient mice present various abnormalities, such as reduced body and brain size, hypersensitivity to seizures, and impaired learning and LTP. These phenotypes are rescued by the introduction of sAPP α in APP-deficient mice, suggesting that sAPP α may play an important role in brain development and function (30).

Compared with sAPP α , little is known about the putative physiological roles of other cleavage products from the non-amyloidogenic and amyloidogenic pathways. However, it has been proposed that A β may regulate synaptic activity, although controversial results have been reported on its beneficial versus



deleterious effects (31, 32). In addition, A β may be involved in the control of cholesterol transport (33) and lipid homeostasis (34). For instance, direct activation of sphingomyelinase and inhibition of hydroxymethylglutaryl-CoA reductase (HMGCR) by A β 1–42 and A β 1–40 have been demonstrated (35). The question of the physiological role of A β remains open, and further studies are clearly needed in this field.

AMYLOID- β AND ITS PRECURSOR IN THE EYE AND RETINA

The retina is a highly specialized neurosensory tissue, which lines the back of the eye. It is an integral part of the brain comprising six different types of neuronal cells and two types of macroglia

cells: retinal Müller glial cells and astrocytes. Retinal and central nervous system (CNS) neurons are derived from common progenitors (36). Differentiated retinal neurons are organized into a well-defined laminar structure and are distributed into three cell and two synaptic layers. The outer segment of the retina is populated by two different types of photoreceptors: cones and rods, which are able to detect light and form the outer nuclear layer (ONL). The detected light signal is transmitted to the cells located at the inner nuclear layer (INL), mainly the bipolar cells followed by retinal ganglion cells (RGCs), either directly or indirectly *via* type II amacrine cells. The latter, together with horizontal cells, modulate glutamatergic neurotransmission along the main synaptic axis comprising photoreceptors, bipolar, and ganglion cells. The principal function of the INL cells is to integrate and regulate

the signal input. The RGC axons converge into the optic nerve fibers, which convey the signal to the visual cortex (37).

To date, the physiological roles of APP in the retina have not been extensively investigated, although a consensus has been met about its expression by retinal pigmented epithelial (RPE) cells in the healthy retina (38). The role of APP in the development of the mouse retina has been recognized such that APP is required for the full differentiation of the AII subtype of amacrine cells. Similar to its role in the brain, APP may be implicated in retinal synaptogenesis. Indeed, APP participates in the developmental determination of the inner plexiform layer (IPL), where amacrine cells synapse to bipolar and ganglion cells (39). Concerning the physiological role of APP in adult mice, it has been shown that APP regulates inner retinal layer function. Indeed, APP-KO mice display alterations in the rod and cone pathways. However, these mice do not present any major deficits in visual function; therefore, APP is not likely a required factor (40). Among all retinal neurons, at least in the rabbit, ganglion cells are the sole cells able to synthesize and express APP on their plasma membrane in the absence of any pathological insult (41). In the human retina, APP expression is age-dependent and was revealed in RGC neurons and the RNFL (42).

Concerning A β , there is no published data on its putative physiological role in the retina. Of interest, the expression of BACE1 has been recently reported in the blood-brain barrier endothelial cells of mouse, bovine, and human origin, thus suggesting putative local production of A β in cerebral blood vessels (43). It remains unknown whether retinal vessel endothelial cells display analogous BACE1 expression. By contrast, BACE1 expression has been reported in the plexiform layer of the rat retina pointing to its synaptic localization (44).

The other parts of the eye have been much less studied in terms of the expression and function of APP and its cleavage products. However, both APP and the proteolytic enzymes involved in its cleavage were found to be expressed in some other eye compartments. For instance, APP and the secretases involved in its processing were identified in the lens (45). Similarly, A β was identified both in the lens (46) and in the vitreous fluid (47).

PATHOLOGICAL ACCUMULATION OF AMYLOID- β : AMYLOIDOSIS, AMYLOIDOPATHY, AND AMYLOIDOGENESIS

Different terms have been associated with the pathological accumulation of A β , with amyloidosis historically being used first. Amyloidosis is a broad term designating a metabolic disease characterized by the extracellular accumulation of globular or natively unfolded or misfolded amyloidogenic polypeptides. Amyloidogenic polypeptides contain a high proportion of β -sheets and have a great propensity to aggregate into highly organized and kinetically stable amyloid fibrils, amorphous aggregates, or oligomers. To date, more than 20 precursor proteins of fibrils (including APP) have been identified in systemic and localized amyloidosis (3). A remarkable property of these fibrils is that, independent of the type of the

precursor protein, they are all 80–100 Å in width. Furthermore, these fibrils organize in a tridimensional β -pleated sheet conformation with the direction of the polypeptide backbone perpendicular to the fibril axis (cross-beta structure). Another remarkable characteristic of amyloidogenic peptides and derived aggregates is their affinity for the Congo red stain (48). The A β -related amyloidopathies consist of increased intra- and/or extracellular accumulation of A β and deposition of A β in the form of insoluble material, such as amyloid plaques or drusen. Several disorders are associated with amyloidopathies, and most of them are neurodegenerative diseases (e.g., AD, PD, polyglutamine diseases, prion disorders, and AMD).

Amyloid-beta is produced *via* the amyloidogenic pathway of APP processing. However, the mechanisms by which this pathway may take over the non-amyloidogenic pathway are poorly understood, especially considering that both pathways coexist in physiological conditions (49). Many genetic and epigenetic factors may be involved, but the evidence points to an increase in the ratio of β - over α -secretase activity as a trigger. This change in the subtle balance between secretase activities in physiological conditions might be associated with the positive control of β -secretase activity by its substrate APP and directly related to APP overexpression and subsequent increase in A β production (50). Over the course of normal aging, A β is deposited subretinally in the mouse and human retina (51). With age, A β accumulates at the interface of the RPE and the photoreceptor outer segment tips. This finding is consistent with increased A β 1–42 secretion by aged human RPE cells (52). As A β accumulates subretinally, microglial cells in normal aged mice become bloated with cellular debris and A β (51). The accumulation of A β in the subretinal space might contribute to the 23–30% reduction in photoreceptors that occurs over human lifetimes (53).

AMYLOID- β AGGREGATION AND TOXICITY

An increase in A β production above normal physiological levels yields cytotoxicity. Among most common A β species (i.e., 1–40 and 1–42 amino acid-containing isoforms), A β 1–42 is considered the most neurotoxic as it is more prone to oligomerization (54). The amyloid aggregation pathway is still poorly understood and several intermediates are likely involved. Small soluble A β monomers can interact to form A β oligomers in the extracellular space. A β oligomers aggregate to form larger fibrils, which in turn aggregate to form extracellular plaques. The mechanisms of A β toxicity are still unclear, and different hypotheses have been proposed. According to the original “amyloid- β cascade hypothesis,” insoluble amyloid fibrils are the main molecular culprit underlying toxicity (55). More recently, this hypothesis has been revised to the “oligomeric amyloid- β hypothesis” (56). It is currently believed that the most toxic intermediates are small oligomers (with degree of polymerization lower than 10), also known as amyloid- β diffusible ligands (ADDL) or protofibrils. The latter have a bigger diffusivity and a larger surface-to-volume ratio that leads to the exposure of hydrophobic patches (57). However, it is not yet clear which oligomeric species is “the most” toxic

since dimers/trimers (58), tetramers (59), and duodecamers such as A β *56 (60) have all been considered as plausible candidates depending on the paradigm (*in vivo*, *in vitro*) or species (murine, human) studied.

Soluble A β oligomers, although they are certainly not involved in all the aspects of AD, are still regarded as key initial triggers of pathogenesis (61). The bioactive pool of soluble A β comprises two fractions: the first is generated in the endosomal compartment and secreted into the extracellular space by exocytosis and the second is intracellular and has been found in both AD patients and animal models of the disease (62, 63). Cellular mechanisms by which soluble oligomers exert neurotoxic effects are multifaceted, involving synaptotoxicity and mitochondrial dysfunction likely related to oxidative stress and metabolic impairment. Insoluble A β aggregates also contribute to A β toxicity either directly through the release of soluble oligomers (64) or indirectly *via* adaptive cellular responses, such as glial and endothelial activation, which can yield neuroinflammation (65) and A β -related angiopathy (66), respectively.

Amyloid- β and Synaptic Dysfunction

One of the prominent facets of A β toxicity concerns synaptic loss (67). This toxicity may be related to a deviation from the A β -associated modulation of synaptic excitability under physiological conditions (31). Indeed, increased synaptic activity may enhance A β release at the synaptic level, reducing excitatory postsynaptic transmission. In particular, it has been shown both *in vitro* and *in vivo*, that A β oligomers reduce glutamatergic synaptic transmission by decreasing the number of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl D-aspartate (NMDA) receptors at the synapse (68–71) (Figure 2A). A decrease in AMPA receptors by A β has been related to increased phosphorylation of the Ca²⁺-permeable subunit, GluR2, and a subsequent increase of intracellular Ca²⁺ levels (72). A decrease in NMDA receptors by A β involves a similar mechanism *via* dephosphorylation of the NR2B subunit and subsequent increase in receptor endocytosis (73). Thus, A β is part of a refined regulatory circuit in which intermediate levels of A β are correlated with a physiological increase in presynaptic activity, whereas lower or higher A β levels are correlated with reduced presynaptic and postsynaptic transmission, respectively (74). Likely, A β differentially affects synaptic activity, depending on synapse type, neuron type, and/or brain region, leading to the imbalance and instability of neuronal networks (75). At the cellular level, A β -mediated alterations involve a shift toward increased excitability manifesting in a decreased resting potential of the neuronal membrane (76). Similarly, the addition of exogenous A β oligomers to hippocampal neurons induced hyperpolarization of the action potential (AP) threshold and decreased after-hyperpolarization (AHP), both compatible with an increase in neuronal excitability (77).

Of note, the vast majority of the above-discussed data has been obtained *in vitro*, by treating cerebral (hippocampal or cortical primary) neurons with soluble A β oligomers. Analogous data for retinal neurons are scarce, although it has been reported that intravitreal injection of A β triggers acute photoreceptor cell death and delayed RGC apoptosis (78). The latter likely involves an

indirect mechanism *via* the activation of Müller cells (78). Finally, a similar A β challenge by intravitreal injection resulted in an impaired pattern of acetylcholine, γ -aminobutyric acid (GABA), and serotonin neurotransmitter expression with catecholaminergic markers being relatively unaffected (79).

Amyloid- β and Mitochondrial Dysfunction

Mitochondrial dysfunction is a common feature of various neurodegenerative diseases and causes alterations in mitochondrial respiratory enzyme complex activities, oxidative stress, opening of mitochondrial permeability transition pores (mPTPs), and enhanced apoptosis (80). In the brain, intracellular A β has been associated with axonopathy and apoptosis initiation (81, 82). Moreover, in neurons, mitochondrial dysfunction is also associated with increased susceptibility to excitotoxicity (i.e., cell death caused by excessive stimulation of neurons by excitatory amino acids, such as glutamate) (83).

Soluble A β peptides have been found in different organelles, and their deleterious effects are largely due to their accumulation within mitochondria. Indeed, intracellular A β inhibits the activity of different mitochondrial respiratory enzymes, causes decreased ATP production, and increases the production of reactive oxygen species (ROS) (84–87) (Figure 2B). Moreover, A β induces mitochondrial dysfunction by interacting with the A β -binding protein known as A β -binding alcohol dehydrogenase (ABAD), which is present on the mitochondrial membrane (88). In addition, A β accumulation impairs the permeability of mitochondrial membranes leading to the opening of mitochondrial Ca²⁺ channels and mPTPs as well as the enhancement of cytochrome *c* (Cyt_c) release (89). At the structural level, accumulation of soluble A β impairs mitochondrial fusion and fission and triggers abnormalities in mitochondrial trafficking, morphology, and degradation [reviewed in Ref. (90)].

In the retina, intraocular injection of respiratory complex (I, III, and IV) inhibitors or A β fibrils yields induction of BACE1 expression and activity, suggesting that A β -mediated mitochondrial respiratory inhibition and oxidative stress facilitate BACE1 expression (44). Interestingly, subretinal injection of A β oligomers resulted in RPE cell hypertrophy without triggering apoptosis but yielded a significant amount of delayed photoreceptor death (91).

Amyloid- β and Glial Activation

The presence of misfolded proteins and their aggregates causes an alteration in the receptor–ligand interactions that modulate both microglia and astroglia activity. Both microglia and astroglia release cytokines, nitric oxide, and other cytotoxic molecules after A β exposure (Figure 2C). Astroglia regulate synapse formation and function in addition to participating in the tripartite synapse (92). It was shown that A β upregulates NF κ B in astrocytes, leading to C3 release (93). The latter binds the neuronal G-protein-coupled receptor C3aR, inducing dendritic structural alterations and synaptic dysfunction. C3 also interacts with microglial C3aR causing alterations in cognitive function and impairment of A β phagocytosis (94). Moreover, the exposure of astroglia to A β , favors astrogliosis, a process that leads to molecular and functional changes in astrocytes and is

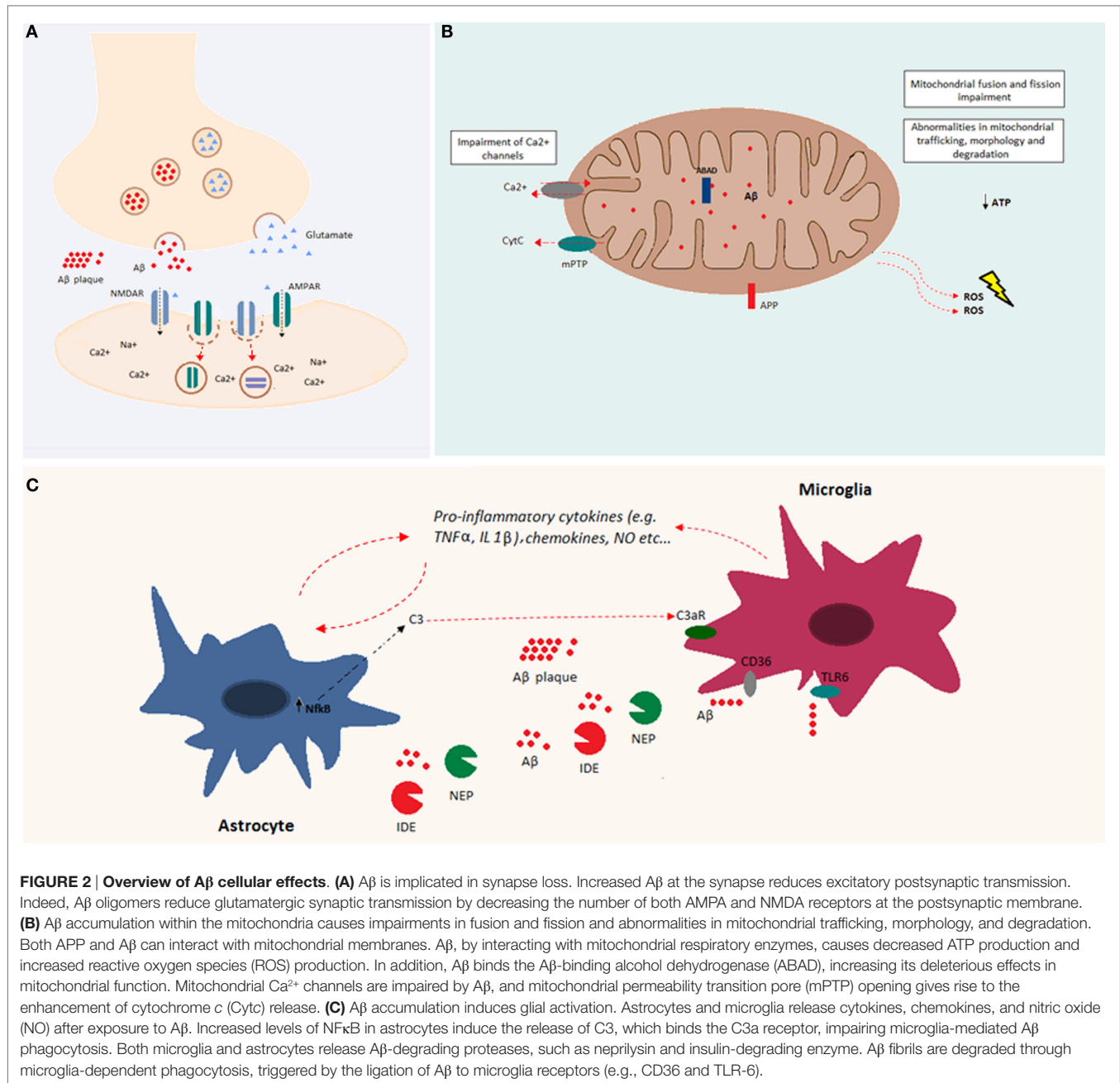


FIGURE 2 | Overview of Aβ cellular effects. (A) Aβ is implicated in synapse loss. Increased Aβ at the synapse reduces excitatory postsynaptic transmission. Indeed, Aβ oligomers reduce glutamatergic synaptic transmission by decreasing the number of both AMPA and NMDA receptors at the postsynaptic membrane. **(B)** Aβ accumulation within the mitochondria causes impairments in fusion and fission and abnormalities in mitochondrial trafficking, morphology, and degradation. Both APP and Aβ can interact with mitochondrial membranes. Aβ, by interacting with mitochondrial respiratory enzymes, causes decreased ATP production and increased reactive oxygen species (ROS) production. In addition, Aβ binds the Aβ-binding alcohol dehydrogenase (ABAD), increasing its deleterious effects in mitochondrial function. Mitochondrial Ca^{2+} channels are impaired by Aβ, and mitochondrial permeability transition pore (mPTP) opening gives rise to the enhancement of cytochrome c (CytC) release. **(C)** Aβ accumulation induces glial activation. Astrocytes and microglia release cytokines, chemokines, and nitric oxide (NO) after exposure to Aβ. Increased levels of NFκB in astrocytes induce the release of C3, which binds the C3a receptor, impairing microglia-mediated Aβ phagocytosis. Both microglia and astrocytes release Aβ-degrading proteases, such as neprilysin and insulin-degrading enzyme. Aβ fibrils are degraded through microglia-dependent phagocytosis, triggered by the ligation of Aβ to microglia receptors (e.g., CD36 and TLR-6).

implicated in different brain diseases (95). Furthermore, astroglia play an important role in Aβ clearance. Indeed, astrocytes are able to bind to and degrade Aβ and release extracellular Aβ-degrading proteases (e.g., neprilysin, insulin-degrading enzyme, angiotensin-converting enzyme-1, and endothelin-converting enzyme-2) (96, 97). On the other hand, microglia are phagocytic cells ubiquitously distributed in the brain. Microglia play important roles in the maintenance and plasticity of neuronal circuits, in the surveillance for pathogens or cell debris, and in tissue maintenance (98–100). Aβ oligomers and fibrils are able to bind microglia surface receptors, such as cluster of differentiation-36 (CD36), toll-like receptor (TLR)-4, and TLR-6, leading to their

activation (101, 102). Activated microglia release proinflammatory cytokines and chemokines (102, 103). Consequently, extracellular proteases (in particular, neprilysin and the insulin-degrading enzyme) are released and give rise to enzymatic degradation of soluble Aβ (104). In addition, receptor ligation triggers the activation of microglial-dependent phagocytosis of Aβ fibrils and their degradation through the endolysosomal pathway. Aβ accumulation itself leads to increased release of proinflammatory cytokines, such as tumor necrosis factor-α (TNFα), interleukin (IL)-1α, and IL-1β (105, 106). The massive release of proinflammatory cytokines might be associated with impairment of synaptic transmission by suppressing LTP

(100). It has also been shown that there is a positive feedback loop between TNF α and A β , since TNF α is able to induce A β production by increasing BACE1 expression and γ -secretase activity (107, 108). In addition, the use of TNF α inhibitors leads to a decrease in APP processing and A β (109). Similarly, IL-1 β increases A β production by increasing γ -secretase activity (107). Even though the early activation of astroglia and microglia is beneficial and leads to A β clearance, in a pathological context, the sustained activation of these cells may induce a positive feedback loop between APP processing and inflammation, which is deleterious (100). Indeed, inflammation is a consequence of A β accumulation, and as a result, inflammation contributes directly to the pathogenesis and progression of the disease.

Amyloid- β and Blood Vessels

The pathophysiological cause and consequence of the accumulation of A β and/or its precursor APP in the brain and the retina remain poorly understood. Twenty years ago, it was reported that coincident APP and B-cell lymphoma-2 (Bcl-2) induction may play a role in rat retinal cell survival after optic nerve and vascular injury. The underlying mechanism involves APP induction selectively in either activated astrocytes (Müller cells) or neurons (110). Microinjection of A β into the adult zebrafish eye triggers an increase in endothelial tip cells and a subsequent increase in the capillary bed density without affecting larger arterial vessels (111). In this light, the recent discovery of BACE1 expression in endothelial cells (indicating local cleavage of APP to A β in the blood–brain barrier in mice, bovine, and humans) has attracted much interest (43). Indeed, BACE1 appears to be a critical regulator of retinal homeostasis since genetic invalidation of BACE1 in mice yields retinal thinning, apoptosis, reduced retinal vascular density, and increased accumulation of the age pigment, lipofuscin (112). The use of BACE1 inhibitors for therapeutic purposes should therefore be carefully evaluated for the putative impairment of retinal homeostasis.

Some aspects of endothelial BACE1 regulation have been elucidated, such as its induction in the presence of reduced levels of microRNA-195 (miR-195) in hypoperfusion/hypoxic conditions (113). This BACE1 induction is associated with reduced occludin expression in tight junctions of cerebral blood vessels (114). The cellular mechanism behind the deleterious effects of A β on cerebral vessel endothelial cells involves activation of the cationic Ca²⁺-permeable channel transient receptor potential melastatin-2 (TRPM-2) and intracellular Ca²⁺ overload (115). In fact, the A β -mediated decrease in zonula occludin-1 (ZO-1) expression is attenuated by neutralizing antibodies against receptor for advanced glycation end-products (RAGE) and inhibitors of calcineurin, suggesting that the A β –RAGE interactions disrupt tight junction proteins *via* the Ca²⁺-calcineurin pathway (116).

A β AMYLOIDOSIS-RELATED RETINAL NEURODEGENERATIVE DISEASES

Accumulation and aggregation of A β is a common denominator of a number of neurodegenerative diseases. Some of them

primarily affect the eye/retina (AMD, glaucoma), while others display more specific cerebral manifestations, such as AD and PD. However, evidence is accumulating in support of retinal alterations that may reflect the cerebral neurodegeneration seen in AD and PD patients.

Alzheimer's Disease

Alzheimer's disease is the main cause of dementia and the most common neurodegenerative disorder in the elderly. It is characterized by cognitive, memory, and language impairments leading to a complete loss of executive functions at the advanced stages (<https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf>). From a histopathological point of view, two main hallmarks of AD are A β plaques and neurofibrillary tangles (NFTs). The latter are mainly composed of hyperphosphorylated tau protein, a microtubule-associated protein (MAP) essential for the maintenance of neuronal polarity and structure (117). It has been shown that A β accumulation leads to disassembly of tau from the microtubules and promotes its hyperphosphorylation (118, 119). The hyperphosphorylation of tau and its subsequent oligomerization results in the formation of intracellular NFTs. Ultimately, cytotoxic NFTs act in synergy with oligomeric A β and lead to synaptic dysfunction and axonal loss (120, 121).

AD Pathology in the Brain

Functional alterations associated with AD have been extensively studied in the brain at different levels (network/circuit, cellular, subcellular, and molecular) of organization.

Synaptic Dysfunction

Amyloid-beta oligomers reduce glutamatergic synaptic transmission by decreasing the number of both AMPA and NMDA postsynaptic receptors (68–71). Besides, a small increase in A β has been correlated with increased presynaptic transmission, implicating the activation of α 7-nicotinic acetylcholine receptors (nAChR) (32, 122). These synaptic dysfunctions coincide with dysregulation of both LTP and long-term depression (LTD), which are attenuated and enhanced, respectively. Such functional impairments are accompanied with a collapse of dendritic spines and synaptic loss (69, 70, 123). Importantly, AD is characterized by aberrant excitatory network activity and synchronization, which leads to dysfunction of learning and memory circuits and subsequent cognitive decline (124).

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction is an early event in AD pathogenesis (87). Both APP (125) and A β (126) are targeted to mitochondria. Mitochondrial A β accumulation has been clearly demonstrated both in AD patients and in transgenic AD mouse models (127, 128). However, the precise mitochondrial actions of A β are still poorly understood. In particular, it is unknown whether mitochondrial translocation of intracellular A β is required for the inhibitory effects on mitochondrial membrane potential (MMP) and ATP levels recently demonstrated in a transgenic mouse AD model (TgAPP/PS1) (129). Besides, it has been suggested that A β cooperates synergistically with tau in the impairment of oxidative phosphorylation (86). Indeed, several mitochondrial

respiratory enzymes were found to be altered in AD, leading to impairments in energy metabolism (130), but the cause–effect relationship between these impairments and A β has not been entirely elucidated.

Neuroinflammation

Prominent glial cell activation and related neuroinflammation are seen at the advanced stages of AD and likely play a pivotal role in AD progression (100). The aggregation of both A β and tau protein leads to the activation of microglia and astroglia, which are consistently found surrounding A β deposits in postmortem AD brains (131–133). More recently, positron emission tomography (PET) brought additional *in vivo* evidence for AD-associated cerebral microgliosis (134).

Accordingly, evidence of neuroinflammation was present in all studied AD mouse models (65). In particular, a prominent induction of TNF α and shift from phagocytic M2 toward the cytotoxic-like M1 microglia phenotype has been reported in the hippocampus at the overt stages of AD pathology in TgAPP/PS1 mice, and this effect was reproduced by treating microglia cultures with oligomeric A β (135). This upregulation is accompanied by the coincident induction of another major proinflammatory cytokine, IL-1 β , not only in the TgAPP/PS1 mouse (136, 137) but also in Tg2576 (138), 3xTg (139), and TgCRND8 (140) mice. Most importantly, all these studies confirmed consistent and concomitant microglia and astrocyte activation.

The microglia M1-like activation state is characterized by uncontrolled proinflammatory cytokine and chemokine secretion, inefficient A β phagocytosis, and TLR activation, which further fuels neuroinflammation (65). Among the relevant cytokines and chemokines, monocyte chemoattractant protein (MCP-1) was repeatedly implicated. The membrane pore-forming capacity of A β oligomers has also been related to neuroinflammation (141). Classically, deleterious neuroinflammatory environments exacerbate AD-related pathological alterations and have been consistently involved in AD progression. However, evidence is mounting to suggest that neuroinflammation likely also occurs before significant A β accumulation (142). Moreover, proinflammatory alterations related to the upregulation of TNF α in the context of partial microglia activation may occur even before A β accumulation (143).

Amyloid Microangiopathy

Microangiopathy, which comprises a host of pathological alterations in the small blood vessels (arterioles, venules, and capillaries), is closely related to cerebral small vessel disease (CSVD). These are heterogeneous pathological conditions that include cerebral blood flow deregulation, endothelial activation, and blood–brain barrier disruption (144).

Such pathological alterations are also found in cerebral amyloid microangiopathy (145). This particular form of microangiopathy results from A β deposition within the walls of capillaries or immediately in the adjacent brain parenchyma (145, 146). According to an emerging concept, these lesions may play a causal role in cerebral dysfunction and precede AD-related cognitive impairments (146). Remarkably, although A β accumulates selectively in arterioles, the cortical vasculature

network appears to be altered in TgCRND8 mice. Extensive structural and functional alterations were observed, including vessel coiling and looping, increased tortuosity of the venules (but not arterioles), and altered microvascular network cerebral blood flow response to hypercapnia (147).

Another prominent feature of AD-related amyloid microangiopathy is the presence of microbleeds. In the Tg2576 mouse model of AD, these microbleeds are due to leakage or rupture of microvasculature in brain regions affected by vascular amyloid deposits (148). Such microbleeds may be related to the upregulation of BACE1 observed in endothelial cells of the blood–brain barrier in another mouse AD model (43) as well as AD patients (114). The knockdown of miR-195, which regulates BACE1 expression at least in endothelial cells, yields increased tau phosphorylation at Ser202/Thr205, Ser262, Thr231, and Ser422, as well as Cdk5/p25 activation in the rat hippocampus (113).

AD Pathology in the Retina

The accumulation of A β and its deposition into A β plaques have been found in postmortem retinas from AD patients (9). In addition, visual disturbances are common in AD, and they may be due to local retinal abnormalities rather than exclusively related to central, visual cortex alterations (149). However, the molecular mechanisms underlying these visual disturbances and the role that A β may play in the retina are still largely unknown. Structural abnormalities identified in retinas of AD patients include reduced number of optic nerve fibers and altered thickness of the parapapillary and macular RNFL (150, 151). These structural changes likely reflect retinal neurodegeneration, such as RGC death (152), and are further associated with optic nerve damage (153).

Consistently, A β plaques have also been found in the retina of AD transgenic mouse models (9). Retinas from APP transgenic mouse strains contain 18–70 kDa proteolytic products from APP. The proportion of α -secretase generated C-terminal fragments in transgenic retinas was higher than the fragments generated from β -secretase. However, in ELISA assays, retinal A β 1–42 was 75 times lower than in transgenic brains and remains undetectable by western blot, indicating that much less A β is generated in the retina compared with the brain (154). The age-dependent increase in plaques in the outer and inner plexiform layers (OPL/IPL), INL/ONL, and ganglion cell layer (GCL) (155) coincides only partly with the upregulation of APP, which is seen only in the RGC and INL regions (149). In line with these data, transgenic AD mice display both neuroinflammation and neurodegeneration mostly in the GCL (152, 156), where they correlate with APP induction and A β accumulation (149).

Interestingly, a recent study showed that amyloidopathy occurs in the retina prior to the brain in TgAPP/PS1 mice, suggesting that in AD patients, A β deposits may also be detected in the retina prior to the brain (10). The study of retinal amyloidopathy may be useful, not only to understand the molecular mechanisms involved in AD but also to search for early-stage AD-related biomarkers. This prospect is even more interesting, considering the possibility of developing a non-invasive method to diagnose early-stage AD through direct retinal imaging.

Synaptic Dysfunction in the Retina

Available data concerning AD-related retinal synaptic dysfunctions come exclusively from electroretinogram (ERG) recordings, which give insight into the global electrical response of the retina to a light stimulus. ERGs performed in AD patients at the advanced stages of pathology revealed a significant reduction in the amplitudes of a- and b-waves as well as an increased latency of the response (156, 157). Analogous data have been reported in the aged TgAPP/PS1 mouse model (155). However, while ERG recordings provide a rough estimate of the AD-dependent impairments in glutamate-mediated excitatory neurotransmission in the retina, they do not decipher the underlying mechanisms. Cellular electrophysiology studies (field-recording, patch-clamp) are needed in order to precisely define the neurochemical type of synapses and neurons that are the main targets of A β .

Neuroinflammation in the Retina

The accumulation of A β deposits with age in the retina of a transgenic mouse model of AD is accompanied by an increase in immunoreactivity for MCP-1 and F4/80, which suggests that resident microglia are activated, as well as an increase in terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive profiles in the GCL (149). These results suggest that A β -induced neurodegeneration is associated with neuroinflammation (149).

The subretinal microinjection of A β yields an adaptive, local inflammatory response, which consists of altered expression patterns of cyclooxygenase-2 (COX-2), glutamine synthetase (GS), inwardly rectifying potassium (Kir) channel Kir4.1, and aquaporin (AQP)-4 water channels in retinal Müller glia cells and of AQP-1 in photoreceptors. Activation of the CCL2/CCR2 chemokine axis, along with microglia activation and migration, is also detectable in this paradigm, whereas its inhibition provides neuroprotection against the deleterious actions of A β (158). Moreover, A β triggers gliosis characterized by glial fibrillary acidic protein (GFAP), vimentin, and nestin upregulation in Müller cells (159). These alterations are similar to those seen during neuroinflammation in the brain.

The upregulation of GFAP was further confirmed after A β injection into the vitreous fluid (160) in both acute (48 h) and delayed (5 months) settings. Remarkably, this study demonstrated a concomitant and selective loss of parvalbumin-expressing neurons in the INL and, to a lower extent, in the GCL (160). The latter finding suggests that, as in the AD brain (161) and transgenic AD mouse models (162, 163), parvalbumin-expressing inhibitory neurons in the retina may be the most vulnerable to A β .

Mitochondrial Dysfunction and Oxidative Stress in the Retina

The neuroinflammation triggered by subretinal injection of A β was accompanied by oxidative stress in the inner and outer retinal segments with an increase in highly reactive unsaturated aldehydes 4-hydroxy 2-nonenal (HNE) and acrolein as well as in 8-hydroxy-2'-deoxyguanosine (8-OHdG), a measure of oxidative damage to DNA (159), which culminated in photoreceptor cell death (158, 159). Accordingly, an inverse approach consisting of intravitreal injection of mitochondrial respiratory

complex inhibitors confirmed that inhibition of mitochondrial function and associated oxidative stress resulted in increased APP processing and A β accumulation. The latter alterations were also found to be accompanied with GFAP upregulation and glial activation (44).

Amyloid Microangiopathy

Amyloid-beta accumulation has been found in the retinal and choroidal vasculature of AD mouse models, suggesting that A β may be implicated in alterations in local blood flow (149). Moreover, retinal veins in AD patients are narrowed, and the retinal blood flow is decreased (164). Most importantly, a very large case-controlled study (213 AD patients and 294 cognitively normal controls) of retinal microvasculature networks reported a significant decrease in the branching pattern index (fractal dimension) of the retinal venular tree and arteriolar tortuosity in patients (165). Taken together, recent studies in the brain and retina point to similar alterations in the microvasculature in mouse models and AD patients. Furthermore, retinal microvasculature alterations, accessible to non-invasive imaging, may reflect those occurring in the brain. In line with this assumption, abnormal retinal blood flow has been correlated with degree of cognitive impairment (AD versus MCI versus control subjects), suggesting that blood flow abnormalities may precede AD-related neurodegeneration (166).

Age-Related Macular Degeneration

Age-related macular degeneration is an age-related retinal degenerative disease that causes irreversible vision loss. It is estimated that up to 50 million people worldwide are affected by AMD, and in western countries 5–10% of individuals over 60 years of age suffer from this disorder (167). AMD is characterized by the build-up of drusen deposits between the Bruch's membrane (BM) and the RPE, which lead to RPE cell abnormalities, dysfunction of the choroidal blood-eye barrier, and photoreceptor death (168, 169). The most common form of AMD is dry AMD, characterized by thickening of the BM, formation of drusen deposits, and activation of the innate immune response (170). The dry form may progress into the exudative (or wet) form, which is characterized by choroidal neovascularization and retinal edema (171). In some cases, drusen deposits continue to expand and can coalesce, giving rise to the degeneration of a large area of RPE and photoreceptors in a process known as geographic atrophy. Drusen is extracellular deposits composed of different proteins, including A β and complement members (172). The mechanism leading to drusen formation is still unclear but may involve the accumulation of toxic by-products of the phototransduction cycle (173). These toxic by-products cause oxidative stress and inflammation, which play a central role in AMD progression (42, 174–177). Drusen-associated amyloidogenic proteins have recently been identified as oligomers (172).

Retinal cells that overlie both soft and hard drusen display numerous structural and molecular abnormalities. Normally detectable only in the outer segments of rod photoreceptors, rod opsin immunolabeling was also observed in the inner segment, cell body, axon, and axon terminal of photoreceptors that overlie drusen (178).

Similar to AD, the risk of developing AMD is also linked to some apolipoprotein E (APOE) polymorphisms. However, in contrast to AD, it has been shown that the $\epsilon 4$ allele of the gene encoding APOE is associated with a lower risk of developing AMD, while the $\epsilon 2$ allele is associated with a higher risk. Other polymorphisms associated with the development of AMD are linked to genes encoding components of the complement system (170). The polymorphism Y402H in complement factor H (CFH), for example, is the first genetic risk factor for both forms of AMD (179–181). It occurs in 33% of individuals and is associated with a 48% risk for developing AMD (182). CFH is the main inhibitor of the alternative pathway, a key component of the innate immune response. *cfh* KO mice also show features of AMD (183). The mechanisms by which CFH and polymorphisms in the gene affect AMD remain unknown. In 2016, the CFH Y402H polymorphism was identified as a risk factor for AD in a very large cohort of patients (184), confirming previous studies (185).

Synaptic Dysfunctions

There is currently no data on putative synaptic dysfunctions in AMD. This may be related to the fact that the main target of neurodegeneration in AMD is the RPE, which is not part of the neuronal network *sensu stricto*. However, RPE cells are excitable, and it would be interesting to explore A β -related effects on their excitability.

Drusen-associated abnormalities in the synaptic terminals of photoreceptor neurons have been reported. In AMD-afflicted retinas, but not in normal aged human retinas, a large number of photoreceptor synapses across the entire retina retract into the ONL. This event evokes the subsequent outgrowth of dendrites from postsynaptic bipolar cells, again across the entire retina, and the subsequent rearrangement of synaptic contacts between the photoreceptor and bipolar cells. In addition, an increase in intermediate filament protein immunoreactivity (vimentin and GFAP) is observed within Müller glial cells in areas of the retina overlying drusen. However, other types of retinal neurons (i.e., bipolar, horizontal, amacrine, and ganglion cells) are all, at least structurally, unaffected (186).

Mitochondrial Dysfunction and Oxidative Stress

In AMD, the accumulation of lipofuscin, i.e., cross-linked pigmented deposits from photoreceptor membranes, favors RPE degeneration. Lipofuscin has damaging oxidant properties and has been associated with mitochondrial dysfunction. Similar to what happens within the brain, A β accumulation may further exacerbate this state of metabolic and oxidative stress (170). Analogously, A β accumulation may contribute to mitochondrial dysfunction in RGCs. Indeed, intracellular A β has also been observed in these cells, and it is likely that A β interferes with mitochondrial function, following the mechanisms characterized in AD (37).

Neuroinflammation

Drusen formation leads to activation of the innate immune system and also to oxidative and metabolic stress, which progressively leads to neurodegeneration. Increased deposition of A β has been found in photoreceptor outer segments and in the

membrane between the RPE and the BM, in the retinas of both aging humans and mice (51). It has been proposed that along with aging, gradual accumulation of debris may initiate the formation of drusen, which encapsulates different types of proteins, lipids, and inflammatory molecules (176). Among these proteins, extracellular A β derived from injured RPE may be included in drusen. Still, the role A β plays in this context is unclear. It has been shown that the oligomeric form of A β 1–42 is implicated in the increased production of ROS, the alteration of RPE cell structure, and transepithelial permeability (91). In addition, A β may enhance the release of vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor from RPE cells, favoring angiogenesis (187).

Amyloid Microangiopathy

Amyloid microangiopathy has not been extensively studied in AMD. However, it has been proposed that microvascular leakage may be caused by the promoting effect that amyloidogenesis may exert on neoangiogenesis. VEGF-mediated angiopathy plays a key role in choroidal neovascularization, which is a hallmark of exudative AMD (188). On the other hand, increased VEGF levels may be triggered by members of the complement system, such as C3a and C5a (189). It remains to be determined what triggers the activation of the complement system. Similar to what happens in AD, A β may promote its activation (190).

The activated complement system may in turn lead to increased vascular permeability and hypervascularization. This scenario has been experimentally verified in aged Tg2576 mice and postmortem AD brain tissue (191). Neovascularization is a major hallmark of exudative AMD, and by consequence, this form of AMD and AD may share pathological mechanisms in the context of blood–brain barrier impairments. However, a recent study (including 107 individuals diagnosed with AMD) reported no difference between venular and arteriolar calibers in the macula region, at least during the early stages of AMD (192) in agreement with a previous study (193).

Glaucoma

Glaucoma is a progressive optic neuropathy that represents one of the leading causes of blindness worldwide. It is characterized by the loss of RGC neurons and their axons, with consequent structural changes in the optic nerve and visual field defects. The entire visual pathway, including intracranial optic nerve, lateral geniculate nucleus, and visual cortex, is affected (5, 194, 195). Therefore, glaucoma can be associated with other neurodegenerative disorders, such as AD, since the most vulnerable neuronal target (i.e., RGCs) is common for both pathologies.

One of the major risk factors for developing glaucoma is chronically elevated intraocular pressure (IOP). Accordingly, it has been shown that elevated IOP leads to ganglion cell changes that promote caspase activation and abnormal APP processing (196). Reducing IOP is the only therapy available to limit disease progression; however, the correlation between glaucoma and IOP has only been partially elucidated, and other factors clearly contribute to its pathogenesis (197, 198). Indeed, reducing IOP does not always stop disease progression (199), and some primary open-angle glaucoma patients show normal IOP (200).

It is presently unknown if A β is among the additional factors involved in the observed changes in IOP during glaucoma. Nevertheless, A β does appear to be a common denominator for glaucoma and AD. Indeed, in glaucoma patients, the level of A β in the vitreous fluid is decreased, while tau protein is increased (201). Similarly, in AD patients, the level of A β in the cerebrospinal fluid (CSF) is decreased, because of its reduced clearance, whereas tau protein is increased (202). In addition, increased levels of A β have been observed in RGCs in rat models of acute ocular hypertension (196, 203). Moreover, inhibiting A β production or improving its clearance reduced RGC death (203).

Synaptic Dysfunction

Mechanisms of synaptic dysfunction in glaucoma have not yet been investigated.

Mitochondrial Dysfunction and Oxidative Stress

Glaucoma has been shown to involve mitochondrial dysfunction (204), and oxidatively modified DNA, proteins, and lipids have been identified in affected patients (205). Importantly, the plasma level of F2-isoprostane lipid was correlated with heat shock protein 72 (HSP72) and heme-oxygenase-1, which are both known to be involved in the defense response against oxidative stress and are increased in glaucoma patients (206).

Neuroinflammation

Transcripts of TNF α , IL-2, and IL-6 have been identified in the iris of neovascular glaucoma patients (207). The role of retinal glia-derived proinflammatory cytokines, notably IL-1 β and TNF α , in glaucoma has been broadly recognized (208). Important insights into neuroinflammation-related mechanisms of glaucoma have been recently obtained in an elegant study using a rat model of glaucoma. The dominant-negative TNF α inhibitor, XPro1595, which selectively inhibits soluble TNF α , rescued Müller cell and microglia/macrophage activation after induction of ocular hypertension. Moreover, XPro1595 also prevented the TNF α -mediated induction of the Ca²⁺-permeable GluR2 subunit of AMPA glutamate receptors, which are known to be causal in the cytotoxic effects of TNF α , as well as in the death of RGC neurons (209). These data formally demonstrate the causal link between neuroinflammation and neurodegeneration in glaucoma.

Amyloid Microangiopathy

To date, putative A β -related structural and functional alterations of microvessels have not been investigated in glaucoma. Indeed, a host of publications (more than 2000 referenced in PubMed) deal with hemodynamic alterations that are consistently found in glaucoma (210). However, endothelin-1 and nitric oxide, known to be released by endothelial cells upon activation, are increased in open-angle glaucoma, suggesting the possible involvement of microvasculature in this pathology (210).

CONCLUSION

Based on the evidence discussed in this review, it is increasingly clear that, at least in the case of A β -amyloidosis, the deleterious effects that A β exerts on both cerebral and retinal neurons are very

similar. These similarities concern alterations at both the cellular and molecular levels, such as cytokine induction and mitochondrial failure, regardless of the particular disease. Furthermore, A β -related alterations, such as oxidative stress, microvasculature abnormalities, and neuroinflammation, are more related to amyloidosis than to the pathological context specific to each disorder (e.g., the different composition of A β plaques and drusen in AD and AMD).

Amyloid-beta may therefore be an attractive common target for immunotherapy in both AMD and AD. Encouraging results were obtained after administration of anti-A β antibodies in mouse models of AMD (211) and AD (212) that motivated human clinical trials, in spite of some secondary effects. Although the first-generation of A β vaccines in AD was interrupted because of severe cerebral hemorrhage (213), new molecules are currently in clinical trials. In particular, GSK933776 was effective in both AMD phase II (214) and AD phase I (215) trials. These clinical data further point to common mechanisms in AD and AMD. Consistently, treatment with an anti-A β antibody in a mouse model of AMD yielded a decrease in A β deposits both in the retina and the brain (211).

At this stage, many challenges remain for the future. For example, it is of utmost importance to determine whether a coincident oligopathy, such as the PD-associated α -synuclein amyloidosis, may affect A β -amyloidosis output in the retina. Understanding whether these two amyloidoses yield additive or synergistic pathological alterations may be very helpful for designing new and more global therapeutic approaches for all relevant diseases.

It is now largely recognized that neurodegenerative alterations in the retina reflect those occurring in the brain, thus raising the hope of using the retina as a source of diagnostic biomarkers for cerebral neurodegeneration. The retina has attracted much interest since, when compared with the brain, it displays the advantage of being relatively less complex structurally and more accessible to non-invasive exploration. Indeed, it may 1 day be possible to use the retina as a proxy to diagnose early neurodegenerative alterations in the brain to target them before neurodegeneration becomes irreversible.

AUTHOR CONTRIBUTIONS

AM wrote the first draft of the manuscript, managed the references, and prepared the **Figure 2**. VD prepared the **Figure 1** and brought constructive changes to the text of the manuscript. CC significantly reviewed the text and worked on references indexing. FM made the major modifications in the course of successive reviewing. SK conceived and supervised the preparation of the review.

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